

EFFECT OF *PIOGLITAZONE* ON INFLAMMATORY MEDIATORS IN TYPE 2 DIABETES

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ABSTRACT : Type 2 Diabetes Mellitus is a metabolic disease associated with a constellation of abnormalities including dyslipidemia, elevated plasma inflammatory markers and hypertension. The effect of *pioglitazone* on inflammatory mediators was analysed in the present study. The study groups consisted of 220 type 2 diabetic patients (110 Males, 110 Females) and 220 age and sex matched *pioglitazone* treated type 2 diabetic subjects (110 Males, 110 Females). The values of CRP, C3, ceruloplasmin, cortisol, alpha 1 antitrypsin and haptoglobin were found to be significantly decreased by *pioglitazone* when compared to type 2 diabetic subjects. The levels of tumour necrosis factor α and interleukin -6 were decreased and adiponectin was found to be remarkably increased in *pioglitazone* treated type 2 diabetic subjects as compared to type 2 diabetic patients. Hence *pioglitazone* therapy serves as an effective approach in restoring immune status in type 2 diabetes mellitus.

KEYWORDS: *Pioglitazone*, type 2 diabetes mellitus, inflammation, mediators.

INTRODUCTION

It is well known that type 2 Diabetes Mellitus particularly when inadequately controlled and accompanied by other risk factors such as hypertension and dyslipidemia predisposes to a number of adverse health consequences including accelerated rates of atherosclerotic cardiovascular disease, renal insufficiency, end stage renal disease, retinopathy and peripheral neuropathy. These complications are responsible for the vast majority of diabetes – related morbidity and mortality and are largely dependent on the detrimental effects of diabetes on vasculature.

Abnormal activation of inflammatory processes is gaining recognition as a possible unifying explanation for the micro vascular and macro vascular injury that occurs in the setting of diabetes. In addition, inflammation is thought to mediate the development of insulin resistance and pancreatic β – cell dysfunction. Markers of inflammation, such as CRP, TNF - α , IL-6 are increased in patients with insulin resistance syndrome. Thiazolidinediones such as *pioglitazone* play an important role in modulating the inflammatory markers (Moore *et al.*, 2001).

MATERIALS AND METHODS

The study groups consisted of uncontrolled type 2 diabetes mellitus patients (n=220, 110 Males, 110 Females) attending the private hospitals in and around Thanjavur of Tamil Nadu. They were freshly diagnosed diabetics and were not under medication for the disease previously. Age and sex matched *pioglitazone* treated type 2 diabetic subjects (n=220, 110 Males, 110 Females) were also selected and analysed as given below.

Serum, plasma and whole blood were utilized for immunological studies. CRP was assayed by Singer *et al* method. Complement 3 was estimated by radial immuno diffusion (Noel. R. Rose *et al.*, 1986). Serum haptoglobin was determined by sandwich ELISA technique. (Levy *et al.*, 2004). Cortisol was estimated by immuno enzymatic method. (Arakawa *et al.*, 1979). Plasma ceruloplasmin was estimated by the Ravin method (1961). The concentration of alpha 1 anti-trypsin was measured by double antibody sandwich enzyme linked immunosorbent assay (Bou Gharios *et al.*, 1999).

Enzyme linked immunosorbent assay was used for the invitro quantitative determination of Interleukin-6 and TNF- α in human serum (Kuleryski, 1981) The amount of plasma adiponectin was estimated by ELISA method. (Pannacciulli *et al.*, 2003).

RESULTS AND DISCUSSION

Inflammatory activation may contribute to the pathogenesis of type 2 DM in part through pancreatic β - cell dysfunction, which occurs on the setting of hyperglycemia. It is clear that β - cell dysfunction continues despite treatment of diabetes with currently available pharmacologic approaches, but thiazolidinediones appear to offer the best means to slow the decline of β - cell function (Kahn *et al.*, 2006)

In addition to the involvement in the development of diabetes itself, inflammatory activation may also be important in diabetic complications such as atherosclerosis, diabetic nephropathy and diabetic retinopathy. The mechanisms through which inflammatory mediators contribute to these processes primarily involves macrovascular and microvascular damage.

There has been a recent explosion of studies showing that important cytokines and adipokines are produced and released from fat tissue. Many of these are pro-inflammatory, but several proteins including adiponectin can have beneficial actions to reduce inflammation and improve endothelial function (Trujillo *et al.*, 2006).

Pioglitazone caused significant reduction in the markers of inflammation - CRP, fibrinogen, C3, ceruloplasmin, haptoglobin and α_1 anti - trypsin. *Pioglitazone* also produces considerable reduction in the values of IL - 6 and TNF - α , the adipocytokine that play a prominent role in the pathophysiology of type 2 diabetes mellitus (Table 1 and 2). The attributable reduction in the levels of the above inflammatory markers were not attributable to glycemic control alone but also mediated by the increase in the levels of adiponectin.

TABLE 1: The levels of inflammatory markers in type 2 diabetic and pioglitazone treated type 2 diabetic subjects

Groups	Treatment	CRP (mg/ml)	C3 (g/l)	Cceruloplasmin (mg/dl)	cortisol (mg/dl)	Haptoglobin (g/l)	Alpha 1 anti-trypsin (mg/dl)
I	Type 2 diabetic subjects	2.14 ± 0.89 ^b	3.355 ± 0.709 ^b	55.38 ± 9.34 ^b	25.63 ± 6.88 ^b	2.93 ± 2.083 ^b	257.83 ± 21.37 ^b
II	Pioglitazone treated type 2 diabetic subjects	0.212 ± 0.703 ^d	1.531 ± 0.407 ^d	25.27 ± 5.572 ^d	8.59 ± 2.70 ^d	1.22 ± 0.593 ^d	147.30 ± 42.80 ^d

Values were expressed in mean ± SD (n =220) . Values not sharing a common superscript significantly differ at P < 0.01 (paired sample t test)

TABLE 2: The levels of IL –6 , TNF – α and Adiponectin in type 2 diabetic and pioglitazone treated type 2 diabetic subjects

Group	Treatment	IL – 6 (pg/ml)	TNF -α (pg/ml)	Adiponectin (pg/ml)
I	Type 2 diabetic subjects	51.47 ± 24.20 ^b	26.39 ± 11.68 ^b	4.928 ± 0.966 ^b
II	Pioglitazone treated type 2 diabetic subjects	0.825 ± 0.39 ^d	5.29 ± 1.74 ^d	153.45 ± 17.34 ^d

Values were expressed in mean ± SD (n =220) . Values not sharing a common superscript significantly differ at P < 0.01 (paired sample t test)

The effects of adiponectin on energy metabolism, insulin sensitivity and atherogenesis are mainly mediated through ability to increase the phosphorylation and activation of AMPK/malonylCOA signaling and to modulate the nuclear factor κβ pathway in metabolically active tissues.(Goldstein and Scalia, 2004). These effects result in increased fatty acid oxidation, increased glucose utilization, reduced endogenous glucose production and subsequently improved insulin sensitivity and circulating carbohydrate and lipid profiles (Chandran *et al.*, 2003 ; Diez and Iglesias , 2003) .

Recently , adiponectin has been shown to be transported through the blood brain barrier to act centrally and to increase energy expenditure and weight loss, combined with a reduction in serum glucose and lipid levels. This effect is partially synergistic with that of leptin and hence is likely to be mediated through a neuroendocrine feedback loop (Qi *et al.*, 2004).

Thus *pioglitazone* prevented coronary arteriosclerosis, possibly by its anti-inflammatory effects. The anti inflammatory and anti arteriosclerotic effects of *pioglitazone* may be mediated by downregulation of CCR 2 in circulating and lesional monocytes. Inhibition of the CCR-2 mediated inflammation may represent novel anti-inflammatory actions of *pioglitazone* beyond metabolic effects.

CONCLUSION

Hence it is concluded that *pioglitazone* was found to modulate the inflammatory responses and possibly attenuate the complications of type 2 diabetes that cause significant morbidity and mortality.

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